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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/801,988	GEORGES ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *8-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 1-77 are pending, and claims 8-77 are withdrawn from consideration as being drawn to a non-elected invention

2. Claims 1-7 are under examination. It is noted that claim 6, as drawn to carcinoma cell is hereby rejoined to the species of ovarian neoplastic cell and that claim 6 will be examined only to the extent that it reads on an ovarian carcinoma cells.

3. Applicant's election with traverse of invention of Group I, claims 1-7, in the reply filed on May 22, 2006 is acknowledged. The election of the species "an ovarian cell", "ovary", and "SKOV-3" is also acknowledged.

The traversal of the restriction requirement is on the grounds that the examination of the inventions of groups I, II, X and XI together would not pose a serious burden. These arguments have been considered but have not be found to be persuasive because, while the searches for each of the different groups would be overlapping with the search for the invention of the other groups, the searches would not be coextensive. In particular, groups X and XI are drawn to methods of detecting whether a test cell is neoplastic and methods of detecting neoplastic cells, respectively, while the inventions of groups I and II are drawn to methods detecting multidrug resistance in a test neoplastic cell and in a patient, respectively. Thus, the searches for groups X and XI would entail a search for any association of triosephosphate isomerase with cancer while the search for groups I and II would entail a search of any association of triosephosphate isomerase with multidrug resistance. Further, the inventions of groups I and II comprise different method steps and thus would necessarily entail non-coextensive searches. Applicant further argues that the requirement for an election of species for a particular cancer cell type or a particular cell line are improper because the species share a common utility and a substantial structural feature common to that utility. This argument has been considered has not been found to be persuasive because although different cancer cell types and cell lines may express one or more than one protein in common, such an expression does not constitute a "substantial

structural feature" given the likelihood of substantial structural differences between different cancer cell types and different cell lines.

The Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on the following pages: page 74, line 27; page 88, line 30; page 104, pages 11-12. Applicant is required to delete the cited embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "greater than" in claim 1 is a relative term which renders the claim indefinite. The term "greater than" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims, as drawn to the elected invention, are as follows:

a method for detecting multidrug resistance or multidrug resistance potential in a test neoplastic cell comprising

(a) measuring a level of triosephosphate isomerase protein in the test neoplastic cell of a given origin or cell type, and

(b) comparing the level of triosephosphate isomerase protein in the test neoplastic cell to the level of triosephosphate isomerase in a nonresistant neoplastic cell of the same origin or cell type,

wherein the test neoplastic cell is multidrug resistant or has multidrug resistance potential if the level of triosephosphate isomerase in the test neoplastic cell is greater

than the level of triosephosphate isomerase in the nonresistant neoplastic cell of the same given origin or cell type (claim 1),

wherein measuring the level of triosephosphate isomerase in the test neoplastic cell comprises contacting a cell extract with an anti-triosephosphate isomerase antibody and measuring the level of antibody bound to cellular triosephosphate isomerase (claim 2),

wherein measuring the level of antibody bound to cellular triosephosphate isomerase is by radiolabel (claim 3),

wherein the test neoplastic cell is an ovarian cell (claim 4),

wherein the nonresistant neoplastic cell is SKOV-3 (claim 5),

wherein the test neoplastic cell is selected from the group consisting of a sarcoma cell and a carcinoma cell (claim 6),

wherein the test neoplastic cell from ovary (claim 7).

The specification teaches that triosephosphate isomerase, normally an intracellular protein, is expressed on the cell surface of neoplastic cells and damaged cells, and that it is expressed still more abundantly on the cell surfaces of multidrug resistant (MDR) neoplastic cells and MDR damaged cells (page 3, lines 5-8) than in non-MDR neoplastic or damaged cells of the same type. The specification also provides working examples that demonstrate that a 27 kDa protein (subsequently identified as a triosephosphate isomerase protein) is differentially expressed in membrane fractions of multidrug resistant tumor cell lines as compared to their drug-sensitive counterparts (Example 1, pages 97-101), that the 27 kDa protein is expressed extracellularly on cell membranes of multidrug resistant tumor cells of a tumor cell line (pages 101-103, Example 2 and Example 4, pages 105-107). The specification also teaches that an analysis of 27 kDa protein separated by two dimensional gel

eletrophoresis indicated that the 27 kDa protein to be triosephosphate isomerase (Example 3, pages 103-105).

The teaching of the specification does not enable the claims and one of skill in the art could not predict that the methods would function as claimed because the teaching of specification that cell surface-expression of triosephosphate isomerase correlates with multidrug resistance in cell lines is not sufficient to establish that cell surface-expression of triosephosphate isomerase would be correlated with multidrug resistance in tumor cells in vivo. Characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of

molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract).

Thus, based on cell culture data, one of skill in the art could not predict that the invention would function as claimed for cells derived from the *in vivo* environment. Further, give the differences between normal cells and cultured cells, it could not be predicted that cultured cells could be used as a control for expression of triosephosphate isomerase for in vivo cells. Thus, one of skill in the art could not predict that cell surface expression of triosephosphate isomerase in cells derived from the in vivo environment could be used to detect multidrug resistant cells, and practice of the invention appears to require undue experimentation.

9. Further, even if the above rejection is overcome, claims 1-7 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting multidrug resistance in a test neoplastic cell, does not reasonably provide enablement for detecting multidrug resistance potential in a test neoplastic cell.

One cannot extrapolate the teaching of the specification to enable the scope of the claims because one of skill in the art could not predict that the invention would function as claimed in detecting multidrug resistance potential in a neoplastic cell. The specification in view of the prior art has not established that the level of cell-surface expressed triosephosphate isomerase is a marker for drug resistance potential in neoplastic cells. In particular, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the use of cell-surface expressed triosephosphate isomerase for identifying drug resistance potential in neoplastic cells. Tockman et al teaches that, prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Pertinent to the instant rejection, there is no evidence presented in the specification or the art of record that the level of cell-surface expressed triosephosphate isomerase is in any way associated with multidrug resistance potential, for example, in humans wherein the use of this marker for determination of multidrug resistance potential is clearly contemplated by the Inventors. Tockman goes on to teach that markers have clear biological plausibility and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored and to link those marker results with subsequent clinical confirmation of, in the instant case, multidrug

resistance. This irrefutable link between marker and acknowledged, in this case, multidrug resistance, is the essence of a valid marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated (p. 2716s, col 2). The specification teaches that this is the first time that a correlation between expression levels of cell surface-expressed triosephosphate isomerase and multidrug resistant neoplastic cells has been reported and clearly states that the results disclosed demonstrate that cell-surface expressed triosephosphate isomerase is a positive marker for multidrug resistant cells. However, given the unexpected nature of the results, given that the specification clearly states that this is the first time that a correlation between expression levels for cell-surface expressed triosephosphate isomerase and multidrug resistant cancer cells, given the well known differences between cultured cell line derived tumor cells and primary tumor cells, given the known artifactual nature of cell lines, and given the art recognized necessity to validate cancer markers in order to determine if they in fact do what is suggested, it cannot be predicted and one of ordinary skill in the art would not believe that it is more likely than not that the invention will function as claimed in the detecting multidrug resistance potential in neoplastic cells. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

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Art Unit 1642